DETAILED ACTION

Response to Amendment and Arguments

1. Claims 29-97 are pending.

Claim 98 has been cancelled.

Claims 29-97 are examined on the merits.

Information Disclosure Statement

2. A listing of reference, D316 in information disclosure statement was not proper. The number 5,399,061 was recited in information disclosure statement submitted June 28, 2007. The correct recitation should be U.S. Patent number 6,399,061.

Withdrawn Grounds of Rejection

Claim Rejections - 35 USC § 112

3. The rejection of claim 98 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in light of the cancellation of the claim.

Claim Rejections - 35 USC § 102

4. The rejection of claims 29, 39-44, 46-50, 55, 65-70, 72-76, 81-89 and 94-97 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application Publication number 2003/0026804 A1 (effective filing date August 11, 1998) has been withdrawn in light of Applicants' arguments set forth on page 12 of the Remarks submitted August 7, 2007. Claim 98 has been cancelled.

Claim Rejections - 35 USC § 103

5. The rejection of claims 29-97 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication number 2003/0026804 A1 (effective filing date August 11, 1998), and further in view of U.S. Patent number 6,090,365 (filed November 18, 1997), McLaughlin et al. (Journal of Clinical Oncology 16(8): 2825-2833, August 1998/ IDS reference B1, submitted October 19, 2004) and Stenbygaard et al. (Breast Cancer Research and Treatment 25: 57-63, 1993) is withdrawn in light of Applicants' arguments set forth in the Remarks submitted August 7, 2007. Claim 98 has been cancelled.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 29-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over IDEC Pharmaceuticals Corp. (1997/ IDS reference D158 submitted July 9, 2007), and further in view of U.S. Patent number 5,843,398 (filed April 26, 1996/ IDS reference D18 submitted July 9, 2007), U.S. Patent Application Publication number 2003/0018014 A1 (effective filing date September 17, 1998) and Stenbygaard et al. (Breast Cancer Research and Treatment 25: 57-63, 1993).

IDEC pharmaceuticals teaches the administration of RITUXAN™ (Rituximab), a CD20 antibody for the treatments of patients with relapsed or refractory CD20 positive cancers in doses of 375 mg/m^2, see page 2, Human section…; and page 6, Indications…section. This administration could be administered in combination with CHOP therapy, see page 2, 3rd paragraph. IDEC pharmaceuticals does not teach said method wherein the human patient has chronic lymphocytic leukemia and the CD20 antibody was administered in the designated dosages, time points and manner listed in the claims and chemotherapeutic agents, chlorambucil, methotrexate, toremifene, tamoxifen and cisplatin. IDEC pharmaceutical also does not teach the patient is refractory to fludarabine.

However, the patent teaches the administration of a CD20 antibody for the treatment of B cell chronic lymphocytic leukemia and several chemotherapeutic agents, see column 6, lines 6-14; column 8, lines 9-16; and Table 1. The publication teaches "while CLL patients may have initial clinical responses to alkylating agents such as ....fludarabine, [it] ultimately [will] become refractory to therapy." Stenbygaard teaches the implementation of chemotherapeutic agents, toremifene and tamoxifen in the treatment of cancer.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer an anti-CD20 antibody in the recited dosages to a patient with CLL, as well as additional chemotherapeutic agents. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings well known in the art, that

dosages of any pharmaceutical composition must be adjusted and optimized. Moreover, one of ordinary skill in the art would have been motivated to administer a therapeutic CD20 antibody to CLL patients (including those refractory to therapy), as well as different chemotherapeutic agents with a reasonable expectation of success by teachings in all documents because CD20 is expressed on 95% of patients with B cell chronic lymphocytic leukemias and a variety of chemotherapeutic agents are typically implemented in methods of cancer treatment, see patent column 8, lines 9-17; and both documents in their entirety. Furthermore, RITUXAN™ has been administered to other B cell patients with relapsed and refractory B cell cancers, see IDEC, page 3, Indications…section.

8. Claims 29-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over McLaughin et al. (Journal of Clinical Oncology 16(8): 2825-2833, August 1998/ IDS reference B1, submitted October 19, 2007), and further in view of U.S. Patent number 5,843,398 (filed April 26, 1996/ IDS reference D18 submitted July 9, 2007), U.S. Patent number 6,090,365 (filed November 18, 1997/ IDS reference D20 submitted July 9, 2007), U.S. Patent Application Publication number 2003/0018014 A1 (effective filing date September 17, 1998) and Stenbygaard et al. (Breast Cancer Research and Treatment 25: 57-63, 1993). McLaughlin teaches a method of treating patients with several types of lymphoma with the administration of a chimeric anti-CD20 monoclonal antibody, rituximab (IDEC-C2B8), see title and Patients and Methods section on page 2826, column 1. All

of the patients were given an antibody dose of 375mg/m^2 intravenously once weekly for a total of four infusions, see abstract and page 2826, column 1, Therapy section. Patients had to have either not responded to primary therapy or relapsed in order to participate in the study, see page 2826, 1st column, Eligibility section. "The initial infusion rate was 50mg/h, with subsequent infusion rate increase...", see cited Therapy section. McLaughin does not teach the method wherein the patient has chronic lymphocytic leukemia, wherein the patient is refractory to fludarabine and the CD20 antibody was administered in the designated dosages, time points and the manner listed in the claims and the said antibody was administered in combination with chemotherapeutic agents, chlorambucil, toremifene, tamoxifen, methotrexate and cisplatin.

However, patent '398 teaches the administration of a CD20 antibody for the treatment of B cell chronic lymphocytic leukemia and several chemotherapeutic agents (chlorambucil, methotrexate, cisplatin and CHOP), column 6, lines 6-14; column 8, lines 9-16; and Table 1. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer an anti-CD20 antibody in the recited dosages to a patient with CLL, and in combination with chemotherapeutic agents. Publication 2003/0018014 teaches "while CLL patients may have initial clinical responses to alkylating agents such as ....fludarabine, [it] ultimately [will] become refractory to therapy." Stenbygaard teaches the implementation of chemotherapeutic agents, toremifene and tamoxifen in the treatment of cancer.

U.S. Patent 6,090,365 teaches the administration of a CD20 antibody

intravenously to a patient in the range from 0.2 to 40 mg/kg, which reads on Applicants' range, see column 10, lines 62-64; and column 29, lines 47-56. The patent also teaches the use of methotrexate and cisplatin, see column 17, Table 1; and column 35, lines 12-20.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings well known in the art, that dosages of any pharmaceutical composition must be adjusted and optimized. Moreover, one of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in both documents because CD20 is expressed on 95% of patients with B cell chronic lymphocytic leukemias and chemotherapeutic agents are typically implemented in method of cancer treatment, see patent column 8, lines 9-17; and both documents in their entirety.

Furthermore, it would have been *prima facie* to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of the publication, McLaughlin and the patent to efficaciously treat cancer. One of ordinary skill in the art would have been motivated to combine the teachings of all the documents because McLaughlin cites there has been "...evidence of synergism between [rituxumab] and some chemotherapeutic agents" to implement targeted immunotherapy and consequently specifically destroy cells associated with a pathogenic condition (i.e. leukemias and lymphomas), see McLaughlin page 2831, column 2, last paragraph; and entire Stenbygaard article.

9. Claims 29-42 and 44-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 5,736,137 (filed November 3, 1993/ IDS reference HR submitted May 19, 2004), and further in view of U.S. Patent number 5,843,398 (filed April 26, 1996/ IDS reference D18 submitted July 9, 2007), U.S. Patent number 6,090,365 (filed November 18, 1997/ IDS reference D20 submitted July 9, 2007) and Stenbygaard et al. (Breast Cancer Research and Treatment 25: 57-63, 1993). U.S. Patent number 5,736,137 teaches the parenteral administration mouse/human chimeric anti-CD20 antibodies for the treatment of a B cell cancer in a range from about 0.001 to about 30 mg/kg, see abstract; column 7, lines 60-67; column 8, lines 16-27. This patent does not teach the method wherein the patient has chronic lymphocytic leukemia, refractory to fludarabine and the CD20 antibody was administered in all the designated dosages and time points listed in the claims and in combination with chemotherapeutic agents, chlorambucil, toremifene, tamoxifen, methotrexate and cisplatin.

However, patent '398 teaches the administration of a CD20 antibody for the treatment of B cell chronic lymphocytic leukemia and several chemotherapeutic agents (chlorambucil, methotrexate, cisplatin and CHOP), column 6, lines 6-14; column 8, lines 9-16; and Table 1. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer an anti-CD20 antibody in the recited dosages to a patient with CLL, as well with chemotherapeutic agents. The publication teaches "while CLL patients may have initial clinical responses to alkylating

agents such as ....fludarabine, [it] ultimately [will] become refractory to therapy." Stenbygaard teaches the implementation of chemotherapeutic agents, toremifene and tamoxifen in the treatment of cancer.

Stenbygaard teaches the administration of toremifine and tamoxifen. U.S. Patent 6,090,365 teaches the administration of a CD20 antibody intravenously to a patient in the range from 0.2 to 40 mg/kg, which reads on Applicants' range, see column 10, lines 62-64; and column 29, lines 47-56. The patent also teaches the use of methotrexate and cisplatin, see column 17, Table 1; and column 35, lines 12-20.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings well known in the art, that dosages of any pharmaceutical composition must be adjusted and optimized. Moreover, one of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in both documents because CD20 (B1 antigen) is expressed on 95% of patients with B cell chronic lymphocytic leukemias and chemotherapeutic agents are typically implemented in method of cancer treatment, see patent column 8, lines 9-17; and both documents in their entirety.

Furthermore, it would have been *prima facie* to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of the publication and the patent to efficaciously treat cancer, as well as different chemotherapeutic agents with a reasonable expectation of success by teachings in all documents because CD20 is expressed on 95% of patients with B cell

chronic lymphocytic leukemias and a variety of chemotherapeutic agents are typically implemented in methods of cancer treatment, see patent column 8, lines 9-17; and all documents in their entirety. One of ordinary skill in the art would have been motivated to combine the teachings of all the documents because synergism between anti-cancer agents is art known to be implemented in targeted immunotherapy and consequently specifically destroy cells associated with cancer, see all documents.

10. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The Examiner works a flexible schedule, however she can normally be reached between the hours of 7:30 am to 6:30 pm, with alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alana M. Harris, Ph.D.
11 April 2008

/Alana M. Harris, Ph.D./

Primary Examiner, Art Unit 1643